PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P33791WO/NCB	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/03758	International filing date *(day/month/year)* 21.08.2003	Priority date *(day/month/year)* 21.08.2002
International Patent Classification (IPC) or both national classification and IPC C07K14/72		
Applicant QUEEN MARY & WESTFIELD COLLEGE et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.02.2004	25.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Tudor, M Telephone No. +49 89 2399-7709

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/03758

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-22 as originally filed

Claims, Numbers

1-13 as originally filed

Drawings, Sheets

1/9-9/9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	12,13
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1-5,11-3
	No:	Claims	6-10

2. Citations and explanations

see separate sheet

Re Item IV

Lack of unity of invention

1. The present application does not satisfy the criterion set forth in Rule 13.1 PCT (unity of invention).

   The claims of the present application relate to a monoclonal antibody directed against a peptide comprising the N-terminal portion of the angiotensin-II type-1 receptor for use in the preparation of a medicament for the treatment of cancer or vascular smooth muscle cell proliferation and the use of said N-terminal portion of the angiotensin-II type-1 receptor for use in the preparation of a medicament for the treatment of cancer or as a vaccine.

   In assessing whether the requirements of unity of invention of an application are met, identification of the technical features that each solution to a technical problem contributes over the prior art (special technical features) must be made. If then a technical relationship between the solutions, involving one or more of the same special technical features, can be recognised, the requirements of unity of invention are said to be met.

   The underlying unifying concept between the different groups of claims is that they all relate to the therapeutic properties of a peptide comprising the N-terminal portion of the angiotensin-II type-1 receptor, i.e. either the peptide itself or antibodies directed against said peptide. However, the first medical use of a peptide comprising the N-terminal portion of the angiotensin-II type-1 receptor is described in WO95/09186 where an antibody against said peptide is disclosed for treating hypertension and for controlling uterine contractions. Therefore, as medical uses of a peptide comprising the N-terminal portion of the angiotensin-II type-1 receptor are already known in the art each further medical use must be considered as a separate invention.

   In light of the above mentioned prior art, the apparent technical problem and the corresponding solutions of the present application can be summarised as follows:

   Problem: To provide further medical uses of a peptide comprising the N-terminal

portion of the angiotensin-II type-1 receptor.

Solution 1, Claims 1, 6, 11 (completely) and, 3-5, 8-10 (partially): The use of a monoclonal antibody directed against a peptide comprising the N-terminal portion of the angiotensin-II type-1 receptor or said peptide comprising the N-terminal portion of the angiotensin-II type-1 receptor in the preparation of a medicament for the treatment of cancer; a method of treating cancer using said monoclonal antibody.

Solution 2, Claims 2 and 7 (completely) and, 3-5, 8-10 (partially): The use of a monoclonal antibody directed against a peptide comprising the N-terminal portion of the angiotensin-II type-1 receptor in the preparation of a medicament for the treatment of vascular smooth muscle cell proliferation; a method of treating vascular smooth muscle cell proliferation using said monoclonal antibody.

Solution 3, Claims 12 and 13: A vaccine composition comprising the N-terminal portion of the angiotensin-II type-1 receptor.

As no technical features can be distinguished which, in the light of the prior art, could be regarded as special technical features on which an unifying concept could be based, there is no single inventive concept underlying the plurality of claimed inventions of the present application.

Therefore, an objection to lack of unity of invention has to be raised under Rule 13.1 PCT. Consequently, a distinction of separate inventions has been made (1-3), based on technical features. The resulting separate inventions, as presently identified, have been grouped according to the order in which they have been claimed.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement.

1. Citations

1.1 The documents mentioned in the International Preliminary Examination Report are numbered as in the International Search Report i.e. D1 corresponds to the first document of the search report etc.

2. Novelty (Article 33(2) PCT)

2.1 The claims of the present application meet the requirements set forth in Article 33(2) PCT because none of the available prior art documents describe the use of a monoclonal antibody directed against the N-terminal portion of the angiotensin-II type I receptor in the preparation of a medicament for either the treatment of cancer or for the treatment of vascular smooth muscle cell proliferation. Neither does the prior art teach the use of the N-terminal portion of the angiotensin-II type I receptor as a vaccine.

3. Inventive step (Article 33(3) PCT)

3.1 Regarding Invention I:

a). The subject-matter encompassed in Invention I does not satisfy the criterion set forth in Article 33(3) PCT because the subject matter of claims 1, 3-6 and 8-11 does not involve an inventive step with respect to the available prior art (Rule 65(1)(2) PCT).

b). Document D4, which is considered to be the closest prior art to the subject-matter of invention I, describes the upregulated expression of the angiotensin-II type-1 receptor (AT1 receptor) in breast hyperplasia and *in situ* carcinoma. On page 253 line 58 to page 254 line 2 it states that the blocking of the AT1 receptor may be therapeutically important in blocking the next step in ductal carcinoma *in situ* of the breast. The difference between D4 and the subject-matter of claim 1 is that the applicants have implemented the suggestion in D4. The apparent technical problem can therefore be considered as to provide a means to block the AT1 receptor in the treatment of cancer. In document D1 on page 5 paragraph 4 to page 6 line 1 its states that by binding to the AT1 receptor a monoclonal antibody (6313/G2, as used in the present application) is able to prevent the angiotensin II-generated IP3 response. Therefore, in order to overcome the apparent technical problem and implement the suggestion in D4, the skilled person would merely have to use the monoclonal antibody described in D1. Since a person skilled in the art would arrive at the subject-matter of claim 1 with a reasonable expectation of success and without any inventive effort said subject-matter does not appear to meet the requirements of Article 33(3) PCT.

c). A similar argument to that raised in 2.2(b) above is applicable, *mutatis mutandis*, to independent claim 6 (Article 33(3) PCT).

d). The dependent claims 3-5 and 8-10 do not add any subject-matter to that of the independent claims to which they refer which would meet the requirements of Article 33(3) PCT.

e). The use of the known N-terminal extracellular fragment of the AT1 receptor as competitor for the binding of angiotensin II would appear to be obvious to the skilled person since the use of receptor extracellular fragments for competitive ligand binding is commonplace in the art. Therefore, the subject-matter of claim 11 also appears to lack an inventive step (Article 33(3) PCT).

3.2 Regarding Invention II:

a). Document D7, which is considered to be the closest prior art to the subject-matter of invention II, describes the upregulated expression of the angiotensin-II type-1 receptor (AT1 receptor) in atherosclerotic aortic tissues. On page 1438, right column, last paragraph, it states that the blocking of the AT1 receptor by antibodies may be therapeutically important in limiting atherosclerosis and preserving vascular reactivity. The difference between D7 and the subject-matter of claim 2 is that the applicants have actually used a monoclonal antibody (6313/G2) to inhibit vascular smooth muscle cell proliferation. The apparent technical problem can therefore be considered as to implement the suggestion in D7, namely, to provide an AT1 receptor blocking antibody for use in the treatment of diseases associated with vascular smooth muscle cell proliferation. Document D2 describes the characterisation of a monoclonal antibody (6313/G2) which binds to the AT1 receptor in vascular smooth muscle cells (page 244, left column, first paragraph; Fig.3). Furthermore, document D1 on page 5 paragraph 4 to page 6 line 1 demonstrates that said 6313/G2 monoclonal antibody is able to prevent the angiotensin II-generated IP3 response. Therefore, in order to overcome the apparent technical problem the skilled person would merely have to use the monoclonal antibody described in both D1 and D2. Consequently, it appears that a person skilled in the art would be able to arrive at the subject-matter of claim 2 with a reasonable expectation of success and without any inventive effort (Article 33(3) PCT).

b). The same objections raised in Item V 2.2(a) is also applicable, *mutatis mutandis*, to the subject-matter of independent claim 7 (Article 33(3) PCT).

c). The dependent claims 3-5 and 8-10 do not add any subject-matter to that of independent claims to which they refer which would meet the requirements of Article 33(3) PCT.

3.3 Regarding Invention III:

a). The subject-matter of Invention III (claims 12 and 13) appears to meet the requirements set forth in Articles 33(2) and (3) PCT since none of the available prior art documents describe or suggest a vaccine composition comprising the N-terminal portion of the AT1 receptor.

4. Industrial applicability (Article 33(4) PCT)

4.1 Claims 1-5,12,13 have industrial applicability (Article 33(4) PCT).

4.2 For the assessment of the present claims 6-10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.